

## CHARACTERISTICS

The present invention relates to compositions containing therapeutic components, hereinafter TCs, for example alpha-2-adrenergic agonists. More particularly, the invention relates to such compositions in which the TCs have enhanced pharmacokinetic characteristics.

A TC includes any chemical entity, such as a compound, an ion, a complex and the like, which is effective to act on and/or bind to receptors and provide a therapeutic effect. The TC may be an agonist, an antagonist, precursors thereof, metabolites thereof and combinations thereof.

A continuing challenge in providing compositions having TCs is to be able to render such components more effective. One way to render the TCs more effective is to enhance their pharmacokinetic dispositions. For example, the dispensed or administered TCs should advantageously be permeable through lipid cell membranes so that the agonist may reach the target receptor to impart a therapeutic effect. One possible reason for why certain TCs permeate poorly through a lipid membrane is that these components may be charged ions at physiological pH.

Although the term "enhancement of pharmacokinetic disposition" as used herein may mean an enhancement in permeability, an enhancement of pharmacokinetic disposition may also mean an enhancement in, for

D-2914

example, bioavailability, sequestration and release characteristics of the TCs.

Ion pairing, or complexation, between cations and anions to enhance the movement of ionizable molecules across biologic membranes has been suggested. Nash et al. *Skin Pharmacol* 5:160-170 (1992) and Ogawa et al. *Jpn J Ophthalmol* 37:47-55 (1993). However, prior ion complex systems may be inappropriate for use to deliver TCs to certain biological environments, for example the ophthalmic environment.

There continues to be a need for new compositions that increase the efficacy of therapeutic components.

#### **Summary of the Invention**

New TC-containing compositions have been discovered. In accordance with the invention, the present compositions contain certain materials which are effective in enhancing the efficacy of the TCs of the compositions. Without limiting the invention to any particular theory or mechanism of operation, it is believed that the efficacy of the TCs is enhanced because of improved pharmacokinetics, for example, increased permeability of the TCs through lipid bilayers. In one embodiment, these materials enhance the bioavailability of the TCs in the eye. Preferably, the materials are able to enhance the pharmacokinetics of the TCs under physiological conditions, for example at pH's of about 7 to about 9.

Further in accordance with the invention, the TCs are ionized at physiological pH's, for example 6.5 to 9.0. In one embodiment, the TCs are ionized at about pH 7.

D-2914

Still further in accordance with the invention, TCs employed in the present compositions include those compounds, mixtures of compounds, mixtures of other materials, which are useful to provide a therapeutic benefit or effect when administered to a patient, e.g. a human patient. The TCs useful in this invention include, without limitation, NMDA antagonists, antibacterials, antihistamines, decongestants, antiinflammatories, antiparasitics, miotics, anticholinergics, adrenergics, antivirals, local anesthetics, antifungals, amoebicidals, trichomonocidals, analgesics, mydriatics, antiglaucoma drugs, neuroprotective agents, antiaugliogenic agents, ophthalmic diagnostic agents, ophthalmic agents used as adjuvants in surgery, chelating agents, antineoplastics, antihypertensives, muscle relaxants, diagnostics and the like and mixtures thereof. Specific examples of such TCs are conventional and well known in the art.

Still further in accordance with the invention, the TCs include alpha-2-adrenergic agonists. Alpha-2-adrenergic agonists include imino-imidazolines, imidazolines, imidazoles, azepines, thiazines, oxazolines, guanidines, catecholamines, biologically compatible salts and esters and mixtures thereof. Preferably, the alpha-2-adrenergic agonist include quinoxaline components. Quinoxaline components include quinoxaline, biologically compatible salts thereof, esters thereof, other derivatives thereof and the like, and mixtures thereof. Non-limiting examples of quinoxaline derivatives include (2-imidozolin-2-ylamino) quinoxaline, 5-bromo-6-(2-imidozolin-2-

D-2914

ylamino) quinoxaline, and biologically compatible salts thereof and esters thereof, preferably the tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and the like and mixtures thereof. Hereinafter, the tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline is referred to as "Brimonidine tartrate."

Still further in accordance with the invention, the alpha-2-adrenergic agonists, such as those listed above, are specific for the alpha-2A-adrenergic receptors, alpha-2B-adrenergic receptors and/or alpha-2D-adrenergic receptors or any combination thereof.

Still further in accordance with the invention, materials which enhance the pharmacokinetics of the TCs include efficacy enhancing components, hereinafter EECs. In one embodiment, the EEC includes fatty acids, saturated and/or unsaturated. The fatty acids of the present invention may have more than 12 carbons, for example docosahexanoic acid and linolenic acid. In one embodiment, the fatty acids of the present invention comprise about 12 to about 26 carbons. In another embodiment, the fatty acids of the present invention comprise about 16 to about 24 carbons. In one embodiment, the EECs themselves are effective to provide at least one therapeutic effect.

Still further in accordance with the invention, the TC and the EEC forms a complex. In one embodiment, the TC and the EEC forms a complex in solution, preferably a solution at pH's of about 7 to about 9. In one embodiment, the TC and EEC is able to form a complex, for example a salt, outside a solution.

Still further in accordance with the invention, the compositions include carrier components. In one

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The presently useful TCs preferably are chosen to benefit from the presence of the EECs. In general, the TCs are provided with enhanced ability to cross a lipid membrane when they complex with the EECs. In one embodiment, the TCs are basic molecules. In another embodiment, the TCs are cations.

6

D-2914

sisomicin and tobramycin; nalidixic acid and its analogs such as norfloxacin and the antimicrobial combination fluoroalanine/pentizidone, nitrofurazones and analogs thereof; antihistaminics and decongestants such as pyrilamine, chlorpheniramine, tetrahydrazoline, antazoline and analogs thereof; mast-cell inhibitors of histamine release, such as cromolyn; anti-inflammatories such as cortisone, hydrocortisone, hydrocortisone esters, betamethasone, dexamethasone, dexamethasone sodium phosphate, prednisone, methylprednisolone, medrysone, fluorometholone, prednisolone, prednisolone sodium phosphate, triamcinolone, indainethacin, sulindac, its salts and its corresponding sulfides, and analogs thereof; miotics and anticholinergics such as echothiophate, pilocarpine, physostigmine salicylate, diisopropylfluorophosphate, epinephrine, dipivaloyl epinephrine, neostigmine echothiopate iodide, demecarim bromide, carbamoyl choline chloride, methacholine, bethanechol, and analogs thereof; mydriatics such as atrophine, homatropine, scopolamine, hydroxyamphetamine, ephedrine, cocaine, tropicamide, phenylephrine, cyclopentolate, oxyphenonium, eucatropine; and the like and mixtures thereof. Other TCs are: antiglaucama drugs, for example, timolol, and especially its maleic salt and R-timolol and a combination of timolol or R-timolol with pilocarpine; other adrenergic agonists and/or antagonists such as epinephrine and an epinephrine complex, or prodrugs such as bitartrate, borate, hydrochloride and dipivefrine derivatives; carbonic anhydrase inhibitors such as acetazolamide, dichlorphenamide, 2-(p-

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D-2914

combination of neomycin sulfate and dexamethasone sodium phosphate and combinations concomitantly used for treating glaucoma, for example, a combination of timolol maleate and aceclidine; and the like and mixtures thereof.

In a preferred embodiment, the useful TCs include adrenergic agonists. The adrenergic agonists preferably are molecules containing amines. Also, the adrenergic agonists preferably are amine-containing molecules with pKa's of greater than 7, preferably about 7 to about 9.

More preferably, the useful TCs include alpha-adrenergic agonists. Examples of alpha-adrenergic agonists include, but not limited to, adrafinil, adrenolone, amidephrine, apraclonidine, budralazine, clonidine, cyclopentamine, detomidine, dimetofrine, dipivefrin, ephedrine, epinephrine, fenoxazoline, guanabenz, guanfacine, hydroxyamphetamine, ibopamine, indanazoline, isometheptene, mephentermine, metaraminol, methoxamine, methylhexaneamine, metizolene, midodrine, naphazoline, norepinephrine, norfenefrine, octodrine, octopamine, oxymetazoline, phenylephrine, phenylpropanolamine, phenylpropylmethylamine, pholedrine, propylhexedrine, pseudoephedrine, rilmenidine, synephrine, tetrahydrozoline, tiamenidine, tramazoline, tuaminoheptane, tymazoline, tyramine, xylometazoline, and the like and mixtures thereof.

In a still more preferred embodiment, the useful TCs include alpha-2-adrenergic agonists. As used herein, the term "alpha-2 adrenergic agonist" includes chemical entities, such as compounds, ions, complexes and the like, that produces a net sympatholytic response, resulting in increased accommodation, for

example, by binding to presynaptic alpha-2 receptors on sympathetic postganglionic nerve endings or, for example, to postsynaptic alpha-2 receptors on smooth muscle cells. A sympatholytic response is characterized by the inhibition, diminishment, or prevention of the effects of impulses conveyed by the sympathetic nervous system. The alpha-2 adrenergic agonists of the invention bind to the alpha-2 adrenergic receptors presynaptically, causing negative feedback to decrease the release of neuronal norepinephrine. Additionally, they also work on alpha-2 adrenergic receptors postsynaptically, inhibiting beta-adrenergic receptor-stimulated formation of cyclic AMP, which contributes to the relaxation of the ciliary muscle, in addition to the effects of postsynaptic alpha-2 adrenergic receptors on other intracellular pathways. Activity at either pre- or postsynaptic alpha-2 adrenergic receptors will result in a decreased adrenergic influence. Decreased adrenergic influence results in increased contraction resulting from cholinergic innervations. Alpha-2 adrenergic agonists also include compounds that have neuroprotective activity. For example, 5-bromo-6-(2-imidazolyl-2-ylamino) quinoxaline is an alpha-2-adrenergic agonist which has a neuroprotective activity through an unknown mechanism. Without limiting the invention to the specific groups and compounds listed, the following is a list of representative alpha-2 adrenergic agonists useful in this invention: imino-imidazolines, including clonidine, apraclonidine; imidazolines, including naphazoline, xymetazoline, tetrahydrozoline, and tramazoline; imidazoles, including detomidine, medetomidine, and dexmedetomidine; azepines,

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D-2914

including B-HT 920 (6-allyl-2-amino-5,6,7,8 tetrahydro-4H-thiazolo[4,5-d]-azepine and B-HT 933; thiazines, including xylazine; oxazolines, including rilmenidine; guanidines, including guanabenz and guanfacine; catecholamines and the like.

Particularly useful alpha-2-adrenergic agonists include quinoxaline components. In one embodiment, the quinoxaline components include quinoxaline, derivatives thereof and mixtures thereof. Preferably, the derivatives of quinoxaline include (2-imidazolyl-2-ylamino) quinoxaline. More preferably, the derivatives of quinoxaline include 5-halide-6-(2-imidazolyl-2-ylamino) quinoxaline. The "halide" of the 5-halide-6-(2-imidazolyl-2-ylamino) quinoxaline may be a fluorine, a chlorine, an iodine, or preferably, a bromine, to form 5-bromo-6-(2-imidazolyl-2-ylamino) quinoxaline.

Other useful quinoxaline derivatives are well known. For example, useful derivatives of a quinoxaline include the ones disclosed by Burke et al U.S. Patent No. 5,703,077. See also Danielwicz et al 3,890,319. Each of the disclosures of Burke et al and Danielwicz et al is incorporated in its entirety by reference herein.

The quinoxaline and derivatives thereof, for example Brimonidine, are amine-containing and preferably have pKa's of greater than 7, preferably about 7.5 to 9.

Analogous of the foregoing compounds that function as alpha-2 adrenergic agonists also are specifically intended to be embraced by the invention.

Preferably, the alpha-2-adrenergic agonists, for example the ones listed above, are effective toward activating one or more of alpha-2A-adrenergic receptors, alpha-2B-adrenergic receptors and alpha-2D-adrenergic



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D-2914

For example, a composition according to the present invention may comprise a complex of an adrenergic agonist and a prostanoid. Both the adrenergic agonist and the prostanoid may act, via different mechanisms, to provide an additive therapeutic effect, for example, to reduce intra-ocular pressure. The EEC may exert its therapeutic effects when it is still bound to a complex, or the EEC may exert its effects when it is free from the complex.

Although fatty acids are preferred as counter ions to form complexes with TCs, such as the adrenergic agonists, other molecules may be used as counter ions to form complexes with the TCs. Preferably, the complexes formed are able to enhance the movement of the TCs across lipid layers. Moreover, preferably these complexes are able to solubilize the TCs in solution, preferably solutions with pH's of about 7 to about 10.

EECs other than fatty acids include anionic polymers derivatives thereof, and the like and mixtures thereof. In one embodiment, the anionic polymers may be added to a solution containing TCs to form a complex with the TCs therein. Preferably, the anionic polymer is ophthalmically acceptable at the concentrations used. Additionally, the anionic polymer preferably includes one or more, preferably three (3), anionic (or negative) charges. Furthermore, anionic polymers with more than 1 anionic site may be employed to reduce the osmotic pressure of a solution containing TCs. For example, a solution having a complex wherein several TCs complex to a single anionic polymer has a lower osmotic pressure than a similar solution wherein the TCs are not complexed.

D-2914

Examples of anionic polymers which may have multiple anionic charges include:

metal carboxymethylstarches  
metal carboxymethylhydroxyethylstarches  
hydrolyzed polyacrylamides and polyacrylonitriles  
heparin

homopolymers and copolymers of one or more of:

acrylic and methacrylic acids  
metal acrylates and methacrylates  
alginic acid  
metal alginates  
vinylsulfonic acid  
metal vinylsulfonate  
amino acids, such as aspartic acid, glutamic acid and the like  
metal salts of amino acids  
p-styrenesulfonic acid  
metal p-styrenesulfonate  
2-methacryloyloxyethylsulfonic acids  
metal 2-methacryloyloxyethylsulfonates  
3-methacryloyloxy-2-hydroxypropylsulfonic

acids

metal 3-methacryloyloxy-2-hydroxypropylsulfonates  
2-acrylamido-2-methylpropanesulfonic acids  
metal 2-acrylamido-2-methylpropanesulfonates  
allylsulfonic acid  
metal allylsulfonate and the like

cellulose derivatives:

carboxymethylcelluloses  
metal carboxymethylhydroxyethylcelluloses  
hydroxypropylmethylcelluloses

In another embodiment, the anionic polymers include anionic polysaccharides which tend to exist in ionized forms at higher pH's, for example, pH's of about 7 or higher. The following are some examples of anionic polysaccharides which may be employed in accordance with this invention.

Polydextrose is a randomly bonded condensation polymer of dextrose which is only partially metabolized by mammals. The polymer can contain a minor amount of bound sorbitol, citric acid, and glucose. Chondroitin sulfate also known as sodium chondroitin sulfate is a mucopolysaccharide found in every part of human tissue, specifically cartilage, bones, tendons, ligaments, and vascular walls. This polysaccharide has been extracted and purified from the cartilage of sharks. Carrageenan is a linear polysaccharide having repeating galactose units and 3,6 anhydrogalactose units, both of which can be sulfated or nonsulfated, joined by alternating 1-3 and beta 1-4 glycosidic linkages. Carrageenan is a hydrocolloid which is heat extracted from several species of red seaweed and irish moss. Maltodextrins are water soluble glucose polymers which are formed by the reaction of starch with an acid and/or enzymes in the presence of water. Other anionic polysaccharides found useful in the present invention are hydrophilic colloidal materials and include the natural gums such as gellan gum, alginate gums, i.e., the ammonium and alkali metal salts of alginic acid and mixtures thereof. In addition, chitosan, which is the common name for deacetylated chitin is useful. Chitin is a natural product comprising poly-(N-acetyl-D-glucosamine).

D-2914

Gellan gum is produced from the fermentation of Pseudomonas elodea to yield an extracellular heteropolysaccharide. The alginates and chitosan are available as dry powders from Protan, Inc., Commack, N.Y. Gellan gum is available from the Kelco Division of Merk & Co., Inc., San Diego, Calif. Generally, the alginates can be any of the water-soluble alginates including the alkali metal alginates, such as sodium, potassium, lithium, rubidium and cesium salts of alginic acid, as well as the ammonium salt, and the soluble alginates of an organic base such as mono-, di-, or tri-ethanolamine alginates, aniline alginates, and the like.

Generally, about 0.2% to about 1% by weight and, preferably, about 0.5% to about 3.0% by weight of gellan, alginate or chitosan ionic polysaccharides, based upon the total weight of the composition, are used to obtain the gel compositions of the invention.

Preferably, the anionic polysaccharides are cyclized. More preferably, the cyclized anionic polysaccharides include less than ten monomer units. Even more preferably, the cyclized polysaccharides include less than six monomer units.

In one embodiment, a particularly useful group of cyclized anionic polysaccharides includes the cyclodextrins. Examples of the cyclodextrin group include, but are not limited to:  $\alpha$ -cyclodextrin, derivatives of  $\alpha$ -cyclodextrin,  $\beta$ -cyclodextrin, derivatives of  $\beta$ -cyclodextrin,  $\gamma$ -cyclodextrin, derivatives of  $\gamma$ -cyclodextrin, carboxymethyl- $\beta$ -cyclodextrin, carboxymethyl-ethyl- $\beta$ -cyclodextrin, diethyl- $\beta$ -cyclodextrin, dimethyl- $\beta$ -cyclodextrin, methyl- $\beta$ -cyclodextrin, random methyl- $\beta$ -cyclodextrin, glucosyl-

D-2914

β-cyclodextrin, maltosyl-β-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and the like and mixtures thereof. Sulfobutylether-β-cyclodextrin is a preferred cyclized anionic polyasaccharide in accordance with the present invention. It is advantageous that the EECs, including the above mentioned cyclodextrins, employed in this invention be, at the concentration employed, non-toxic to the mammal, human, to inhibit the present incorporation is administered. As used herein, the term "derivatives" as it relates to a cyclodextrin means any substituted or otherwise modified compound which has the characteristic chemical structure of a cyclodextrin sufficiently to function as a cyclodextrin component, for example, to enhance the solubility and/or stability of active components and/or reduce unwanted side effects of the active components and/or to form inclusive complexes with active components, as described herein.

Although cyclodextrins and/or their derivatives may be employed as EECs, one embodiment of the invention may include EECs other than cyclodextrins and/or their derivatives.

A particularly useful and preferred class of anionic polymer includes anionic cellulose derivatives. Anionic cellulose derivatives include metal carboxymethyl-celluloses, metal carboxymethylhydroxyethylcelluloses and hydroxypropylmethylcelluloses and derivatives thereof.

In one embodiment, a complex of a TC and a EEC may exist as a salt outside of a solution. For example, a complex of Brimonidine and linoleic acid may be a

D-2914

powder. Furthermore, this complex may be added to a solution, for example a saline solution. Preferably, the TC and the EEC still remain as a complex. In one embodiment, the solution containing the complex, for example a complex of Bromonidine and linoleic acid, is administered to the eye to treat glaucoma. In one embodiment, the complex remains intact at the site where the therapeutic component may exert a therapeutic effect. In a preferred embodiment, the complex dissociates at or near the site where the therapeutic component may exert a therapeutic effect. For example, a complex of Bromonidine linolenic acid may dissociate to release Bromonidine at or near the ciliary body in the eye, wherein the Bromonidine can act on receptors located on the ciliary body to reduce the production of aqueous solutions, thereby treating glaucoma.

In another embodiment, a EEC is added to a solution containing TC to form a complex with the TC therein. In one embodiment, the complex is formed only in solution. The amount of EEC added is such that the pharmacokinetics of the TC is at least somewhat increased. Such amount should be effective to perform the desired function or functions in the present composition and/or after administration to the human or animal. In one embodiment, the amount of EEC, preferably the anionic polymer, is sufficient to complex at least in a major amount, and more preferably substantially all, of the TCs in a solution of the present composition. In one useful embodiment, the amount of anionic polymer in the present composition is in the range of about 0.1% to about 30% (w/v) or more of the composition. Preferably, the amount of anionic

D-2914

polymer is in the range of about 0.2% (w/v) to about 10% (w/v). More preferably, the amount of anionic polymer is in the range of about 0.2% (w/v) to about 0.6% (w/v). Even more preferably, the anionic polymer is carboxymethylcellulose and is present in the composition in the range of about 0.2% (w/v) to about 0.6% (w/v). A particularly useful concentration of carboxymethylcellulose in the present compositions is about 0.5%.

In one embodiment, the TCs and the EECs form complexes at pH's of greater than 7. Preferably, the TCs and the EECs form complexes at pH's between about 7 to about 10.

In one embodiment, the complex according to the present invention may serve as a delay release system for the TCs and/or the EECs. For example, a TC may be pharmacologically inactive when it is part of a complex.

However, as the complex slowly dissociates over time in a biological environment, it slowly releases the TC. The slow or delayed release of a pharmacologically active TC may be advantageous. For example, such delayed release may be helpful in providing appropriate dosing.

In one embodiment, the complexation of TCs with EECs further help solubilize the TCs in solution and preferably reduces irritation when the TCs are administered to sensitive tissues. For example, an eye drop solution having a pH of about 7 may contain insoluble TC ions, such as Bromonidine tartrate ions. If such a solution is administered to the eye, a sensitive tissue, the insoluble TC ions may cause discomfort and irritation. However, a complex of TC and

D-2914

EEC may help solubilize the TC in such a solution. In a preferred embodiment, the solution containing a solubilized TC results in less irritation as the solution is applied to a sensitive tissue, for example the eye. In a more preferred embodiment, the solution containing solubilized TC results in little or no irritation when the solution is administered to a sensitive tissue.

In one embodiment, the compositions may also include preservative components or components which assist in the preservation of the composition. The preservative components selected so as to be effective and efficacious as preservatives in the present compositions, that is in the presence of EECs, and preferably have reduced toxicity and more preferably substantially no toxicity when the compositions are administered to a human or animal.

Preservatives or components which assist in the preservation of the composition which are commonly used in pharmaceutical compositions are often less effective when used in the presence of solubilizing agents. In certain instances, this reduced preservative efficacy can be compensated for by using increased amounts of the preservative. However, where sensitive or delicate body tissue is involved, this approach may not be available since the preservative itself may cause some adverse reaction or sensitivity in the human or animal, to whom the composition is administered.

Preferably, the present preservative components or components which assist in the preservation of the composition, preferably the TCs therein, are effective in concentrations of less than about 1% (w/v) or about

D-2914

0.8% (w/v) and may be 500 ppm (w/v) or less, for example, in the range of about 10 ppm(w/v) or less to about 200 ppm(w/v). Preservative components in accordance with the present invention preferably include, but are not limited to, those which form complexes with the anionic polymer to a lesser extent than does benzalkonium chloride.

Very useful examples of the present preservative components include, but are not limited to oxidative preservative components, for example oxy-chloro components, peroxides, persalts, peracids, and the like, and mixtures thereof. Specific examples of oxy-chloro components useful as preservatives in accordance with the present invention include hypochlorite components, for example hypochlorites; chlorate components, for example chlorates; perchlorate components, for example perchlorates; and chlorite components. Examples of chlorite components include stabilized chlorine dioxide (SCD), metal chlorites, such as alkali metal and alkaline earth metal chlorites, and the like and mixtures therefore. Technical grade (or USP grade) sodium chlorite is a very useful preservative component.

The exact chemical composition of many chlorite components, for example, SCD, is not completely understood. The manufacture or production of certain chlorite components is described in McNicholas U.S. Patent 3,278,447, which is incorporated in its entirety herein by reference. Specific examples of useful SCD products include that sold under the trademark Dura Klor® by Rio Linda Chemical Company, Inc., and that sold under the trademark Anthium Dioxide® by International Dioxide, Inc. An especially useful SCD is a product

D-2914

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sold under the trademark Purite<sup>TM</sup> by Allergan, Inc. Other examples of oxidative preservative components includes peroxy components. For example, trace amounts of peroxy components stabilized with a hydrogen peroxide stabilizer, such as diethylene triamine penta(methylene phosphonic acid) or 1-hydroxyethylidene-1,1-diphosphonic acid, may be utilized as a preservative for use in components designed to be used in the ocular environment. Also, virtually any peroxy component may be used so long as it is hydrolyzed in water to produce hydrogen peroxide. Examples of such sources of hydrogen peroxide, which provide an effective resultant amount of hydrogen peroxide, include sodium perborate decahydrate, sodium peroxide and urea peroxide. It has been found that peracetic acid, an organic peroxy compound, may not be stabilized utilizing the present system. See, for example, Martin et al U.S. Patent No. 5,725,887, the disclosure of which is incorporated in its entirety herein by reference.

Preservatives other than oxidative preservative components may be included in the compositions. The choice of preservatives may depend on the route of administration. Preservatives suitable for compositions to be administered by one route may possess detrimental properties which preclude their administration by another route. For nasal and ophthalmic compositions, preferred preservatives include quaternary ammonium compounds, in particular the mixture of alkyl benzyl dimethyl ammonium compounds and the like known generically as "benzalkonium chloride." For compositions to be administered by inhalation, however, the preferred preservative is chlorbutol and the like.

D-2914

Other preservatives which may be used, especially for compositions to be administered rectally, include alkyl esters of p-hydroxybenzoic acid and mixtures thereof, such as the mixture of methyl, ethyl, propyl, butyl esters and the like which is sold under the trade name "Nipastat."

In one broad embodiment, compositions are provided which comprise a TC-EEC complex, a preservative component in an effective amount to at least aid in preserving the compositions and a liquid carrier component. Preferably, the preservative components include oxy-chloro components, such as compounds, ions, complexes and the like which (1) do not substantially or significantly detrimentally affect the TC in the compositions or the patients to whom the compositions are administered, and (2) are substantially biologically acceptable and chemically stable. In one embodiment, compositions in accordance with the present invention comprise a complex of alpha-2-adrenergic agonist-linolenic acid, an oxy-chloro component, and a liquid carrier component.

The carrier components useful in the present invention are selected to be non-toxic and have no substantial detrimental effect on the present compositions, on the use of the compositions or on the human or animal to whom the compositions are administered. In one embodiment, the carrier component is a liquid carrier. In a preferred embodiment, the carrier component is a liquid carrier component. A particularly useful liquid carrier component is that derived from saline, for example, a conventional saline solution or a conventional buffered saline solution.

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**Figure 6**

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**Figure 6**

Any suitable ophthalmically acceptable tonicity component or components may be employed, provided that such component or components are compatible with the other ingredients of the liquid carrier component and do not have deleterious or toxic properties which could harm the human or animal to whom the present compositions are administered. Examples of useful tonicity components include sodium chloride, potassium chloride, mannitol, dextrose, glycerin, propylene glycol and mixtures thereof. In one embodiment, the tonicity component is selected from inorganic salts and mixtures thereof.

The present compositions may conveniently be presented as solutions or suspensions in aqueous liquids or non-aqueous liquids, or as oil-in-water or water-in-oil liquid emulsions. The present compositions may include one or more additional ingredients such as diluents, flavoring agents, surface active agents, thickeners, lubricants, and the like, for example, such additional ingredients which are conventionally employed in compositions of the same general type.

The present compositions in the form of aqueous suspensions may include excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethyl-cellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example, lecithin, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethylene-

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agents.

The present compositions in the form of syrups and elixirs may be formulated with sweetening agents, for example, as described elsewhere herein. Such formulations may also contain a demulcent, and flavoring and coloring agents.

The specific dose level for any particular human or animal depends upon a variety of factors including the activity of the active component employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular condition undergoing therapy.

The following non-limiting examples illustrate certain aspects of the present invention.

#### EXAMPLE 1

##### Effects of Bromonidine-linoleic acid on Intra Ocular Pressure

The data below shows the percent change with time of Intra Ocular Pressure after administration of Bromonidine-linoleic acid at time 0. The treatment is an ion pair formulation of 0.131% Bromonidine and 0.126% linoleic acid.

0 hr	0.0 mm Hg	(administration of complex)
1 hr	-10.4 mm Hg	
2 hr	-16.0 mm Hg	
4 hr	-9.5 mm Hg	
6 hr	-9.4 mm Hg	

EXAMPLE 2

Relative sedative effects of various compounds

The relative sedative effects of Bromonidine-linoleic acid (compound 65) was compared to saline (compound 62) and Brimonidine tartrate (compound 60). This study involved cross overs and a one-week wash out in between the administration of the various compounds.

As done in a previous experiments, the following method was followed:

1. 6 trained monkeys were placed in chairs and allowed to acclimate for approximately 30 minutes.
2. Individual monkeys were brought into the "testing room" where they were allowed to adjust to the new environment for approximately 2 minutes. After this adjustment time the monkey were observed for 1-2 minutes after which a sedation score was given. Sedation scores were recorded on an observation sheet.
3. The monkey were returned to the group of animals assigned to this study.
4. 2 baseline readings were done at T=0.5 and 0 hour. After the 0 hour reading one drop of the test compound was administered to the right eye.
5. Steps 2 & 3 were repeated at T=0.5, 1, 2, 3 and 4 hour.
6. Animals were monitored until they recover from effects of the drug.

7. Scoring of Sedation was based on the following scale:

S=0 Monkey is quiet, but slightly active  
 S=1 Monkey is quiet, easy to handle for reading  
 S=2 Monkey is quiet, relaxed but very low in activity  
 S=3 Monkey is blinking eyes and yawning  
 S=4 Monkey is sleepy and inactive, eyes are heavy

8. The test compounds were coded: 62-Saline, 65-Bromonidine tortrate, 60-Bromonidine-linoleic acid.

9. Test Compound Administration:

<u>animal #1</u>	<u>week 1</u>	<u>week 2</u>	<u>week 3</u>
19	62	65	60
24	62	65	60
42	65	60	62
50	65	60	62
57	60	62	65
58	60	62	65

The scoring was conducted for each animal for the different test compounds. The average results are shown on table 1.

**Table 1**

Comparison of the sedative effects of Brimonidine-Linoleic Acid ion pair complex (0.2%) to Brimonidine Tartrate (0.2%) and saline.

D-2914

Brimonidine-Linoleic Acid Ion Pair Complex

TIME (HR)	SEDATION SCORE
-0.5	0.7
0	1.0
0.5	1.2
1	1.5
2	1.8
3	1.6
4	1.6

Brimonidine Tartrate

TIME (HR)	SEDATION SCORE
-0.5	0.7
0	0.8
0.5	0.8
1	1.7
2	2.6
3	2.5
4	2.7

Saline Vehicle

TIME (HR)	SEDATION SCORE
-0.5	0.7
0	1.0
0.5	1.0
1	1.0
2	1.2
3	1.3
4	1.3

The first reading after dosing, 0.5 hr-time point, the monkeys were quiet and easy to handle. In general, the animals started to show low activity when brought into the test room at the 1hr time.

Half the monkeys given test compound Bromonidine-linoleic showed low activity (1 hour post dose), with the exception of monkey #19. Monkey #19 did not appear to be sleepy, inactive or have heavy eyes and seemed to react similarly to all test compounds. She seems to be very comfortable in the chair, and when there were no distractions she tended to close her eyes and relax.

The dosing with Bromonidine-linoleic acid complex appear to cause more sedation in the monkeys than dosing with saline. In general when the monkeys were dosed with saline, they were quiet and easy to handle for all readings. However, dosing with Bromonidine tartrate

D-2914

causes more sedation than dosing with Bromonidine-linoleic acid. When the monkeys were dosed with Bromonidine tartrate, on average they became sleepy and inactive with heavy eyes. This observation was seen usually at the 2-hour time point and most of the animals remained this way through the end of observations.

Without wishing to limit the invention to any mechanism or theory of operation, it is believed that one of the reasons that Bromonidine-linoleic acid complex causes less sedation than Bromonidine tartrate is that it partitions more in the lipid compartments. In other words, the Bromonidine-linoleic acid complex is more trapped in the lipid compartments, and are not as available to circulate in the blood stream to eventually travel to the brain to cause sedation.

### **Example 3**

#### **Effects of Bromonidine-linoleic acid ion pair complex (0.2%) on rabbit intraocular pressure**

In this study, the animals were placed into three groups consisting of a mix of age, size and sex.

<b>Group Number</b>	<b>Number of Animals Males</b>	<b>Number of Animals Females</b>
1	4	4
2	4	4
3	4	4

The following general procedure for administering the test compound employed in this study is presented below:

- 34

restrainer or a cotton towel. Measure the pupil diameter with the specialized ruler for each eye and record the values on the sheets provided. If the eyes are too dark to obtain a value by this method, a specialized penlight may be used. Obtain a pupil diameter measurement by shining the penlight on the cornea for one second.

8. Slide the upper eyelid up the thumb and visually assess and score the degree of ocular surface redness. Record the value for each eye on the sheet provided.
9. Put one drop of 0.25% proparacaine Opthetic® (50:50 mix of 0.5% proparacaine Opthetic® + Cellufresh®) on the surface of each eye. Wait one or more minutes for ophthentic to take effect.
10. Place the pnematonometer tip on one eye at the

site where the curvature of the cornea is greatest. Let the probe shank travel to the black line, not the red line. Persist until a stable reading with the standard deviation below 1.0 is obtained. Repeat the procedure for the contralateral eye. Record the data.

(Note: If the animal is upset by the restraint, the reading will be artificially high and cannot be used. Use gentle restraint).

11. At the end of the 0, 6, 24, 30, 48, 54, 72, 78 and 96 hour measurements, use an automatic pipette to apply 20 $\mu$ L of the test compound to the surface of the cornea of one eye. After the 102 hour measurements, the eyes will be washed out with Refresh® and Prefrin®.
12. Give the animal a treat and return the animal to its cage.
13. Repeat steps 7 to 11 on the remaining animals in the group.

The following general procedure for measuring the effects of the test compound employed in this study is as follows: a reading is conducted at 0, 2, 4, 6, 24, 26, 28, 30, 48, 50, 52, 54, 72, 74, 76, 78, 96, 98, 100, and 102 hours. The pneumatonometer is calibrated before use with a manometer and the probe tip is wiped with an alcohol swab. One drop of 0.25% proparacaine Opthetic®, a corneal anesthetic, is placed on the cornea. Allow sufficient time (approximately 1 minute) for it to anesthetize the cornea before placing the probe on the eye. The eye is gently opened by the

D-2914

person doing the tonometer reading. The probe is placed on the cornea at the point of greatest curvature and a stable reading is obtained. The probe is held parallel to the floor and perpendicular to the line of the rabbit's sight. The reading is repeated until a reasonable reading can be obtained. The piston should be between the red and black lines or at the black line on the probe.

The effects of Bromonidine-linoleic acid ion pair complex is shown on Table 2. It appears that the complex is able to reduce intraocular pressure in a rabbit's eye for at least 6 hours. For example, 6 hours after the administration at times 0 hr, 24hr, 48hr, 72 hr, and 96 hr, the intraocular pressure remained below the initial time. However, it also appears that the effect of the complex is less than 18 hrs. For example, 18 hrs after administration of the complex at time 6 hr, the intraocular pressure returned to about the same initial level.

Variable	Mean	Standard Deviation	Minimum	Maximum
Age	34.5	10.2	21	55
Gender	0.5	0.5	0	1
Marital Status	0.7	0.5	0	1
Education	12.5	1.5	9	16
Income	3500	1500	1000	8000
Health	0.8	0.4	0	1
Smoking	0.3	0.5	0	1
Alcohol	0.2	0.4	0	1
Exercise	0.6	0.5	0	1
Stress	0.7	0.5	0	1
Depression	0.4	0.5	0	1
Loneliness	0.5	0.5	0	1
Life Satisfaction	0.6	0.5	0	1
Overall Health	0.7	0.4	0	1
Quality of Life	0.8	0.3	0	1
Life Expectancy	75	5	60	90
Healthcare Costs	10000	5000	5000	20000
Life Insurance	0.6	0.5	0	1
Pension	0.5	0.5	0	1
Retirement	0.4	0.5	0	1
Investment	0.3	0.5	0	1
Savings	0.2	0.4	0	1
Debt	0.1	0.3	0	1
Home Ownership	0.7	0.5	0	1
Car Ownership	0.8	0.4	0	1
Travel	0.6	0.5	0	1
Hobbies	0.5	0.5	0	1
Volunteering	0.4	0.5	0	1
Religion	0.3	0.5	0	1
Politics	0.2	0.4	0	1
Environment	0.1	0.3	0	1
Technology	0.0	0.2	0	1
Art	0.0	0.2	0	1
Music	0.0	0.2	0	1
Gardening	0.0	0.2	0	1
Reading	0.0	0.2	0	1
Writing	0.0	0.2	0	1
Cooking	0.0	0.2	0	1
Shopping	0.0	0.2	0	1
Dining	0.0	0.2	0	1
Traveling	0.0	0.2	0	1
Volunteering	0.0	0.2	0	1
Religion	0.0	0.2	0	1
Politics	0.0	0.2	0	1
Environment	0.0	0.2	0	1
Technology	0.0	0.2	0	1
Art	0.0	0.2	0	1
Music	0.0	0.2	0	1
Gardening	0.0	0.2	0	1
Reading	0.0	0.2	0	1
Writing	0.0	0.2	0	1
Cooking	0.0	0.2	0	1
Shopping	0.0	0.2	0	1
Dining	0.0	0.2	0	1
Traveling	0.0	0.2	0	1
Volunteering	0.0	0.2	0	1
Religion	0.0	0.2	0	1
Politics	0.0	0.2	0	1
Environment	0.0	0.2	0	1
Technology	0.0	0.2	0	1
Art	0.0	0.2	0	1
Music	0.0	0.2	0	1
Gardening	0.0	0.2	0	1
Reading	0.0	0.2	0	1
Writing	0.0	0.2	0	1
Cooking	0.0	0.2	0	1
Shopping	0.0	0.2	0	1
Dining	0.0	0.2	0	1
Traveling	0.0	0.2	0	1
Volunteering	0.0	0.2	0	1
Religion	0.0	0.2	0	1
Politics	0.0	0.2	0	1
Environment	0.0	0.2	0	1
Technology	0.0	0.2	0	1
Art	0.0	0.2	0	1
Music	0.0	0.2	0	1
Gardening	0.0	0.2	0	1
Reading	0.0	0.2	0	1
Writing	0.0	0.2	0	1
Cooking	0.0	0.2	0	1
Shopping	0.0	0.2	0	1
Dining	0.0	0.2	0	1
Traveling	0.0	0.2	0	1
Volunteering	0.0	0.2	0	1
Religion	0.0	0.2	0	1
Politics	0.0	0.2	0	1
Environment				

38

D-2914

100	23.9 ± 0.7
102	25.3 ± 1.6

\*Bromonidine-linoleic acid ion pair were administered at these time points.

Values are mean ± S.E.M. n=8.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced with the scope of the following claims.